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<b>UTILITY PATENT APPLICATION TRANSMITTAL</b>  <small>(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))</small>	Attorney Docket No. <u>0/96198US</u>
	First Inventor or Application Identifier <u>Anna M.H. BOOTS</u>
	Title <u>Novel Peptides Suitable for use in Antigen</u>
	Express Mail Label No. <u>EL 087180144 US</u>

Specific  
Immuno-  
Suppressiv  
Therapy

<b>APPLICATION ELEMENTS</b> <small>See MPEP chapter 600 concerning utility patent application contents.</small>	<b>ADDRESS TO:</b> Assistant Commissioner for Patents Box Patent Application Washington, DC 20231
1. <input checked="" type="checkbox"/> * Fee Transmittal Form (e.g., PTO/SB/17) <small>(Submit an original and a duplicate for fee processing)</small> 2. <input checked="" type="checkbox"/> Specification [Total Pages <u>78</u> ] <small>(preferred arrangement set forth below)</small> - Descriptive title of the invention - Cross References to Related Applications - Statement Regarding Fed sponsored R & D - Reference to Microfiche Appendix - Background of the invention - Brief Summary of the invention - Brief Description of the Drawings (if filed) - Detailed Description - Claim(s) - Abstract of the Disclosure 3. <input type="checkbox"/> Drawing(s) (35 U.S.C. 113) [Total Sheets <u>    </u> ] 4. Oath or Declaration [Total Pages <u>2</u> ] a. <input type="checkbox"/> Newly executed (original or copy) b. <input checked="" type="checkbox"/> Copy from a prior application (37 C.F.R. § 1.63(d)) <small>(for continuation/divisional with Box 16 completed)</small> i. <input type="checkbox"/> <b>DELETION OF INVENTOR(S)</b> Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b)	5. <input type="checkbox"/> Microfiche Computer Program (Appendix) 6. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary) a. <input type="checkbox"/> Computer Readable Copy b. <input type="checkbox"/> Paper Copy (identical to computer copy) c. <input type="checkbox"/> Statement verifying identity of above copies
<b>ACCOMPANYING APPLICATION PARTS</b>	
7. <input type="checkbox"/> Assignment Papers (cover sheet & document(s)) 8. <input type="checkbox"/> 37 C.F.R. §3.73(b) Statement <input type="checkbox"/> Power of Attorney (when there is an assignee) 9. <input type="checkbox"/> English Translation Document (if applicable) 10. <input checked="" type="checkbox"/> Information Disclosure Statement (IDS)/PTO-1449 <input type="checkbox"/> Copies of IDS Citations 11. <input checked="" type="checkbox"/> Preliminary Amendment 12. <input checked="" type="checkbox"/> Return Receipt Postcard (MPEP 503) (Should be specifically itemized) 13. <input type="checkbox"/> * Small Entity Statement filed in prior application, (PTO/SB/09-12) Status still proper and desired 14. <input type="checkbox"/> Certified Copy of Priority Document(s) (if foreign priority is claimed) 15. <input type="checkbox"/> Other:	

\* NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

16. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment:  
☐ Continuation ☒ Divisional ☐ Continuation-in-part (CIP) of prior application No. 09 / 171,705  
 Prior application information: Examiner P. Nolan Group / Art Unit 1644  
 For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. CORRESPONDENCE ADDRESS

☐ Customer Number or Bar Code Label or ☒ Correspondence address below

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Signature	Mary E. Gormley	Date	9/8/2000

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JC890 U.S. PTO  
09/657757

09/08/00

# FEE TRANSMITTAL

## for FY 2000

Patent fees are subject to annual revision.  
Small Entity payments must be supported by a small entity statement,  
otherwise large entity fees must be paid. See Forms PTO/SB/09-12.  
See 37 C.F.R. §§ 1.27 and 1.28.

TOTAL AMOUNT OF PAYMENT (\$ 690.00

### Complete if Known

Application Number	To be assigned
Filing Date	September 8, 2000
First Named Inventor	Anna M.H. BOOTS
Examiner Name	To be assigned
Group / Art Unit	To be assigned
Attorney Docket No.	0/96198US

### METHOD OF PAYMENT (check one)

1. ☒ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:

Deposit Account Number 02-2334

Deposit Account Name Akzo Nobel Patent

☒ Charge Any Additional Fee Required Under 37 CFR §§ 1.18 and 1.17

2. ☐ Payment Enclosed:

☐ Check ☐ Money Order ☐ Other

### FEE CALCULATION

#### 1. BASIC FILING FEE

Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description	Fee Paid
101	890	201	345	Utility filing fee	690.00
106	310	206	155	Design filing fee	
107	480	207	240	Plant filing fee	
108	690	208	345	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) (\$ 690.00

#### 2. EXTRA CLAIM FEES

Total Claims 17 -20\*\* = 3 X Fee from below = Fee Paid  
Independent Claims 2 -3\*\* = 1 X Fee from below = Fee Paid  
Multiple Dependent Claims 14 X Fee from below = Fee Paid

\*\*or number previously paid, if greater; For Reissues, see below

Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description
103	18	203	9	Claims in excess of 20
102	78	202	39	Independent claims in excess of 3
104	260	204	130	Multiple dependent claim, if not paid
109	78	209	39	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$ )

### FEE CALCULATION (continued)

#### 3. ADDITIONAL FEES

Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	380	216	190	Extension for reply within second month	
117	870	217	435	Extension for reply within third month	
118	1,360	218	680	Extension for reply within fourth month	
128	1,850	228	925	Extension for reply within fifth month	
119	300	219	150	Notice of Appeal	
120	300	220	150	Filing a brief in support of an appeal	
121	260	221	130	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,210	241	605	Petition to revive - unintentional	
142	1,210	242	605	Utility issue fee (or reissue)	
143	430	243	215	Design issue fee	
144	580	244	290	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	690	246	345	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	690	249	345	For each additional invention to be examined (37 CFR § 1.129(b))	

Other fee (specify) \_\_\_\_\_

Other fee (specify) \_\_\_\_\_

\* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$ )

### SUBMITTED BY

Name (Print Type)	Mary E. Gormley	Registration No. (Attorney/Agent)	34,409	Complete (if applicable)	Telephone (301) 948-7400
Signature	Mary E. Gormley	Date	9/8/2000		

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Express Mail NO. EL 087180144US

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the application of:

Anna M.H. BOOTS and Gilbertus F. M. VERHEIJDEN

Serial Number: To be assigned    Group Art Unit: To be assigned

Filed: Concurrently herewith    Examiner: To be assigned

For: NOVEL PEPTIDES SUITABLE FOR USE IN ANTIGEN SPECIFIC  
IMMUNOSUPPRESSIVE THERAPY

Corresponding to: USSN 09/171,705, filed October 23, 1998

PRELIMINARY AMENDMENT

Commissioner for Patents  
Washington, D.C. 20231

September 8, 2000

Sir:

Prior to the calculation of the fee in the above-identified application, please make the following amendments:

IN THE SPECIFICATION:

Page 1, line 5, please insert the heading -- FIELD OF THE INVENTION --; and

line 11, please insert the heading -- BACKGROUND OF THE INVENTION --.

Page 4, line 4, please insert the heading -- SUMMARY OF THE INVENTION --; and

line 14, please insert the heading -- DETAILED DESCRIPTION OF THE INVENTION --.

Please delete pages 28 - 75 in their entireties. (A new sequence listing is submitted with this application). Please renumber pages 76 --78 as pages 28 - 30.

Page 76 (original), line 1, please delete "CLAIMS" and insert  
-- WE CLAIM: --.

IN THE CLAIMS:

Please delete Claim 1 without prejudice or disclaimer of the  
subject matter thereof.

Claim 2, line 1, please delete "Peptide" and replace with -- A  
peptide --; please delete "consisting of" and replace with --  
having --; and please delete "said"; and  
line 2, please delete "peptide".

Page 77, line 1, please delete "or" and replace with  
-- and --.

Claim 3, line 1, please delete "Peptide" and replace with  
-- The peptide --; and please delete "1 or" and "said peptide";  
line 8, please delete "or" and replace with -- and --.

Claim 4, line 1, please delete "Peptide" and replace with  
-- The peptide --; and please delete "any of claims 1 to" and  
insert therefor - claim --; and please delete "said peptide"; and  
line 5, please delete "or" and insert -- and --.

5. (amended) The peptide [Hexadecapeptide] according to claim 3  
[1 to 4 said], which is a hexadecapeptide [consisting of one of  
the amino acid sequences YKLVCYYTSWSQYREG (SEQ ID NO:1),  
YTSWSQYREGDGSCFP (SEQ ID NO:2), LDRFLCTHIIYSFANI (SEQ ID NO:5),  
THIIYSFANISNDHID (SEQ ID NO:6), PNLKTLLSVGGWNFGS (SEQ ID NO:12),  
QHLDIFISIMTYDFHGA (SEQ ID NO:30), SPLFRGQEDASPDRFS (SEQ ID NO:34),  
DYAVGYMLRLGAPASK (SEQ ID NO:37), MLRLGAPASKLVMGIP (SEQ ID NO:38),  
YLKDRQLAGAMVWALD (SEQ ID NO:54) or LAGAMVWALDLDDFQG (SEQ ID  
NO:55)].

Please cancel claim 6 without prejudice or disclaimer of the subject matter thereof.

7. (amended) A pharmaceutical [Pharmaceatical] composition comprising one or more peptides according to claim 2 [any of the claims 1 to 5[]], and a pharmaceutically [pharmaceutical] acceptable carrier.

Please delete Claims 8 and 9 without prejudice or disclaimer of the subject matter thereof.

Please add the following new claims:

-- 10. A pharmaceutical composition comprising one or more peptides according to claim 5, and a pharmaceutically acceptable carrier. --

-- 11. A test kit for use in the detection of activated autoreactive T cells, comprising one or more peptides according to claim 2. --

-- 12. A test kit for use in the detection of activated autoreactive T cells, comprising one or more peptides according to claim 5. --

-- 13. A pharmaceutical composition comprising one or more peptides selected from the group consisting of peptides containing 16 to 55 amino acid residues and comprising at least one of the amino acid sequences YKLVCCYYTSWSQYREG (SEQ ID NO:1), YTSWSQYREGDGSCFP (SEQ ID NO:2), LDRFLCTHIIYSFANI (SEQ ID NO:5), THIIYSFANISNDHID (SEQ ID NO:6), PNLKTLLSVGGWNFGS (SEQ ID NO:12), NTQSRRTFIKSVPPFL (SEQ ID NO:16), TFIKSVPPFLRTHGFD (SEQ ID NO:17), PPFLRTHGFDGLDLAW (SEQ ID NO:18), HGFDGLDLAWLYPGRR (SEQ ID NO:19), DLAWLYPGRRDKQHFT (SEQ ID NO:20), TIDSSYDIAKISQHLD (SEQ ID NO:28), DIAKISQHLD FISIMT (SEQ ID NO:29), QHLD FISIMTYDFHGA (SEQ ID NO:30),

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SPLFRGQEDASPD RFS (SEQ ID NO:34), DYAVGYMLRLGAPASK (SEQ ID NO:37), MLRLGAPASKLVMGIP (SEQ ID NO:38), PASKLVMGIPTFGRSF (SEQ ID NO:39), GTLAYYEICDFLRGAT (SEQ ID NO:46), EICDFLRGATVHRTL G (SEQ ID NO:47), RGATVHRTL GQQVPYA (SEQ ID NO:48), VKSKVQYLKDRQLAGA (SEQ ID NO:53), YLKDRQLAGAMVWALD (SEQ ID NO:54), LAGAMVWALDLDDFQG (SEQ ID NO:55), WALDLDDFQGSFCGQD (SEQ ID NO:56) or DFQGSFCGQDLRFPLT (SEQ ID NO:57). --

-- 14. A pharmaceutical composition comprising one or more peptides selected from the group consisting of peptides containing 16 to 55 amino acid residues and comprising at least one of the amino acid sequences YKLVCYYTSWSQYREG (SEQ ID NO:1), YTSWSQYREGDGSCFP (SEQ ID NO:2), LDRFLCTHIIYSFANI (SEQ ID NO:5), THIIYSFANISNDHID (SEQ ID NO:6), QHLDFISIMTYDFHGA (SEQ ID NO:30), SPLFRGQEDASPD RFS (SEQ ID NO:34), DYAVGYMLRLGAPASK (SEQ ID NO:37), MLRLGAPASKLVMGIP (SEQ ID NO:38), YLKDRQLAGAMVWALD (SEQ ID NO:54) and LAGAMVWALDLDDFQG (SEQ ID NO:55). --

-- 15. A method of inducing systemic immunological tolerance, comprising administering to a patient in need thereof a pharmaceutical composition comprising one or more peptides selected from the group consisting of peptides containing 16 to 55 amino acid residues and comprising at least one of the amino acid sequences LVCYYTSYS (SEQ ID NO:60), FLCTHIIYS (SEQ ID NO:61), IIYSFANIS (SEQ ID NO:62), LKTLLSVGG (SEQ ID NO:63), FIKSVPPFL (SEQ ID NO:66), YDIAKISQH (SEQ ID NO:67), LDFISIMTY (SEQ ID NO:68), FISIMTYDF (SEQ ID NO:69), FRGQEDASP (SEQ ID NO:70), YAVGYMLRL (SEQ ID NO:71), MLRLGAPAS (SEQ ID NO:72), LAYYEICDF (SEQ ID NO:73), LRGATVHRT (SEQ ID NO:74), YKLDRQLAG (SEQ ID NO:75), LAGAMVWAL (SEQ ID NO:76), VWALDLDDF (SEQ ID NO:77) or LDLDDFQGS (SEQ ID NO:78), and a pharmaceutically acceptable carrier. --

-- 16. A method for inducing systemic immunological tolerance, comprising administering to a patient in need thereof a pharmaceutical composition according to claim 13. --

-- 17. A method for inducing systemic immunological tolerance, comprising administering to a patient in need thereof a pharmaceutical composition according to claim 14. --

#### REMARKS

The specification and claims 2 - 5 and 7 are amended, claims 1, 6 and 8 - 9 are canceled, and claims 10 - 17 are added, hereby. Claims 2 - 5, 7 and 10 - 17 are presented for examination.


In a telephone conference with Ex. Nolan in the parent application, he indicated that the subject matter now presented in claim 15 would be examined with the other claims in this application.

Please use the CRF of record in the parent application for this application. The CRF and Sequence Listing presented herewith are the same, and no new matter is added hereby.

It is believed that claims 2 - 5, 7 and 10 - 17 recite a patentable improvement in the art. Favorable action is

solicited. In the event any fees are required with this paper,  
please charge our Deposit Account No. 02-2334.

Respectfully submitted,

  
Mary E. Gormley  
Attorney for Applicants  
Registration No. 34,409

Attorney Docket NO.O/96198 US/D1  
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NOVEL PEPTIDES SUITABLE FOR USE IN ANTIGEN SPECIFIC  
IMMUNOSUPPRESSIVE THERAPY

5

The invention relates to peptides and their use in treatment of chronic destruction of articular cartilage in autoimmune diseases, pharmaceutical compositions comprising said peptides, a diagnostic method for the detection of autoreactive T cells in  
10 a test sample and test kits to be used in said method.

The immune system is established on a principle of discrimination between foreign antigens (non-self antigens) and autoantigens (self antigens, derived from the individuals own body) achieved by a build in tolerance against the autoantigens.  
15

The immune system protects individuals against foreign antigens and responds to exposure to a foreign antigen by activating specific cells such as T- and B lymphocytes and producing soluble factors like interleukins, antibodies and complement factors. The antigen to which the immune system responds is degraded by the antigen presenting cells (APCs) and a fragment of the antigen is expressed on the cell surface associated with a major histocompatibility complex (MHC) class II glycoprotein. The MHC-glycoprotein-antigen-fragment complex  
20 is presented to a T cell which by virtue of its T cell receptor recognizes the antigen fragment conjointly with the MHC class II protein to which it is bound. The T cell becomes activated, i.e. proliferates and/or produces interleukines, resulting in the expansion of the activated lymphocytes directed to the antigen  
25 under attack (Grey et al., Sci. Am., 261:38-46, 1989).

Self antigens are also continuously processed and presented as antigen fragments by the MHC glycoproteins to T cells (Jardetsky et al., Nature 353:326-329, 1991). Self recognition  
30

thus is intrinsic to the immune system. Under normal circumstances the immune system is tolerant to self antigens and activation of the immune response by these self antigens is avoided.

5 When tolerance to self antigens is lost, the immune system becomes activated against one or more self antigens, resulting in the activation of autoreactive T cells and the production of autoantibodies. This phenomenon is referred to as autoimmunity. As the immune response in general is destructive, i.e. meant to  
10 destroy the invasive foreign antigen, autoimmune responses can cause destruction of the body's own tissue.

The contribution of T cells to autoimmune diseases has been established by several studies. In mice, experimental autoimmune  
15 encephalomyelitis (EAE) is mediated by a highly restricted group of T cells, linked by their specificity for a single epitope of myelin basic protein (MBP) complexed to an MHC class II molecule. In the Lewis rat, a species with high susceptibility to various autoimmune diseases, disease has been  
20 shown to be mediated by T cells.

In humans autoimmune diseases are also thought to be associated with the development of auto-aggressive T cells. A destructive autoimmune response has been implicated in various diseases such as rheumatoid arthritis (RA), in which the  
25 integrity of articular cartilage is destroyed by a chronic inflammatory process. The mere presence of cartilage appears necessary for sustaining the local inflammatory response: it has been shown that cartilage degradation is associated with the activity of cartilage-responsive autoreactive T cells in RA  
30 (Sigall et al., Clin. Exp. Rheumat. 6:59, 1988; Glant et al., Biochem. Soc. Trans. 18:796, 1990; Burmester et al., Rheumatoid arthritis Smolen, Kalden, Maini (Eds) Springer-Verlag Berlin

Heidelberg, 1992). Furthermore, removal of cartilage from RA patients by surgery was shown to reduce the inflammatory process. The cartilage proteins are therefore considered to be target autoantigens which are competent of stimulating T cells. 5 Activation of these autoreactive T cells leads to development of autoimmune disease. Hence it can be anticipated that functional elimination of these T cells could be beneficial in downregulation of the destructive autoimmune process. However, the identification of the autoantigenic components that play a role in the onset of rheumatoid arthritis has so far remained elusory. 10

The inflammatory response resulting in the destruction of the cartilage can be treated by various drugs. However, these 15 drugs are immunosuppressive drugs that are nonspecific and have toxic side effects. The disadvantages of nonspecific immunosuppression makes this a highly unfavourable therapy.

Antigen-specific, nontoxic immunosuppression, such as for instance described in WO-A-9510301, provides a very attractive 20 alternative for nonspecific immunosuppression. The antigen-specific therapy involves the treatment of patients with synthetic T cell-reactive peptides which resemble or mimic the epitopes present on the autoantigen. These peptides can therefore be used to induce systemic immunological tolerance, 25 i.e. specific T cell tolerance, both to themselves and to the autoantigen. The induced systemic immunological tolerance is based on the long-observed phenomenon that animals which have been fed or have inhaled an antigen or epitope are less capable of developing a systemic immune response towards said antigen or 30 epitope when said antigen or epitope is introduced via a systemic route. To effectively use the peptide-induced systemic tolerance therapy to treat the T cell mediated cartilage

destruction, there is a great need for T cell-reactive peptides which can desensitize patients against the self antigen that is activating the T cells responsible for the inflammatory process.

5 It is an object of the invention to provide peptides which are able to induce systemic immunological tolerance, more in particular specific T cell tolerance, to the responsible cartilage antigen in patients suffering from T cell-mediated cartilage destruction. It is another object of the invention to provide a method for detecting autoreactive T cells involved in the destruction of articular cartilage and test kits to be used in said method.

10 The present invention provides for such peptides.

In a first aspect of the invention there is provided for peptides consisting of 16 to 55 amino acid residues, said peptide comprising at least one of the amino acid sequences  
20 LVCYYTWS (SEQ ID NO:60), FLCTHIIYS (SEQ ID NO:61), IIYSFANIS (SEQ ID NO:62), LKTLLSVGG (SEQ ID NO:63), FIKSVPPFL (SEQ ID NO:64), FDGLDLAWL (SEQ ID NO: 65), LYPGRDKQ (SEQ ID NO:66), YDIAKISQH (SEQ ID NO:67), LDFISIMTY (SEQ ID NO:68), FISIMTYDF (SEQ ID NO:69), FRQEDASP (SEQ ID NO:70), YAVGYMLRL (SEQ ID NO:71), MLRLGAPAS (SEQ ID NO:72), LAYYEICDF (SEQ ID NO:73),  
25 LRGÄTVHRT (SEQ ID NO:74), YLKDRQLAG (SEQ ID NO:75), LAGAMVWAL (SEQ ID NO:76), VWALDLDDF (SEQ ID NO:77) or LDLDDFQGS (SEQ ID NO:78).

In particular, the peptide according to the invention comprises at least one of the amino acid sequences  
30 YKLVCYYTWSQYREG (SEQ ID NO:1), YTWSQYREGDGSCFP (SEQ ID NO:2), LDRFLCTHIIYSFANI (SEQ ID NO:5), THIIYSFANISNDHID (SEQ ID NO:6), PNLKTLLSVGGWNFGS (SEQ ID NO:12), NTQSRRTFIKSVPPFL (SEQ ID

NO:16), TFIKSVPPFLRTHGFD (SEQ ID NO:17), PPFLRTHGFDGLDLAW (SEQ ID NO:18), HGFDGLDLAWLYPGRR (SEQ ID NO:19), DLAWLYPGRRDKQHFT (SEQ ID NO:20), TIDSSYDIAKISQHLD (SEQ ID NO:28), DIAKISQHLD FISIMT (SEQ ID NO:29), QHLD FISIMTYDFHGA (SEQ ID NO:30), SPLFRGQEDASPDRFS (SEQ ID NO:34), DYAVGYMLRLGAPASK (SEQ ID NO:37), MLRLGAPASKLVMGIP (SEQ ID NO:38), PASKLVMGIPTFGRSF (SEQ ID NO:39), GTLAYYEICDFLRGAT (SEQ ID NO:46), EICDFLRGATVHRTL (SEQ ID NO:47), RGATVHRTL GQQVPYA (SEQ ID NO:48), VKSKVQYLKDRQLAGA (SEQ ID NO:53), YLKDRQLAGAMVWALD (SEQ ID NO:54), LAGAMVWALDLDDFQG (SEQ ID NO:55), WALDLDDFQGSFCGQD (SEQ ID NO:56) or DFQGSFCGQDLRFPLT (SEQ ID NO:57).

Preferably, the peptide according to the present invention comprises one of the amino acid sequences YKLVCYYTWSQYREG (SEQ ID NO:1), YTWSQYREGDGSCFP (SEQ ID NO:2), LDRFLCTHIIYSFANI (SEQ ID NO:5), THIIYSFANISNDHID (SEQ ID NO:6), PNLKTLLSVGGWNFGS (SEQ ID NO:12), QHLD FISIMTYDFHGA (SEQ ID NO:30), SPLFRGQEDASPDRFS (SEQ ID NO:34), DYAVGYMLRLGAPASK (SEQ ID NO:37), MLRLGAPASKLVMGIP (SEQ ID NO:38), YLKDRQLAGAMVWALD (SEQ ID NO:54) or LAGAMVWALDLDDFQG (SEQ ID NO:55).

More preferably, the peptide according to the invention comprises one or more of the amino acid sequences YTWSQYREGDGSCFP (SEQ ID NO:2), SPLFRGQEDASPDRFS (SEQ ID NO:34), MLRLGAPASKLVMGIP (SEQ ID NO:38), YLKDRQLAGAMVWALD (SEQ ID NO:54) or LAGAMVWALDLDDFQG (SEQ ID NO:55).

The peptides according to the invention consist of 16 to 55, preferably 16 to 35, more preferably 16 to 25, most preferably 16 amino acid residues.

Highly preferred peptides according to the invention are hexadecapeptides consisting of the amino acid sequence YKLVCYYTWSQYREG (SEQ ID NO:1) YTWSQYREGDGSCFP (SEQ ID NO:2), LDRFLCTHIIYSFANI (SEQ ID NO:5), THIIYSFANISNDHID (SEQ ID NO:6), PNLKTLLSVGGWNFGS (SEQ ID NO:12), QHLD FISIMTYDFHGA (SEQ ID

NO:30), SPLFRGQEDASPDERS (SEQ ID NO:34), DYAVGYMLRLGAPASK (SEQ ID NO:37), MLRLGAPASKLVMGIP (SEQ ID NO:38), YLKDRQLAGAMVWALD (SEQ ID NO:54) or LAGAMVWALDLDDFQG (SEQ ID NO:55), more in particular the amino acid sequences YTSWSQYREGDGSCFP (SEQ ID NO:2), SPLFRGQEDASPDERS (SEQ ID NO:34), MLRLGAPASKLVMGIP (SEQ ID NO:38), YLKDRQLAGAMVWALD (SEQ ID NO:54) or LAGAMVWALDLDDFQG (SEQ ID NO:55).

Also within the scope of the invention are multimers of the peptides according to the invention such as for example a dimer or trimer of the peptides according to the invention. A multimer according to the invention can either be a homomer, consisting of a multitude of the same peptide, or a heteromer consisting of different peptides.

The characteristic amino acid sequences of the peptides according to the invention can be flanked by random amino acid sequences. Preferred are flanking sequences, that have a stabilizing effect on the peptides, thus increasing their biological availability.

The present invention is based on the unexpected discovery, that Human Cartilage glycoprotein 39 (herein after referred to as HC gp-39) is a target autoantigen in RA patients which activates specific T cells, thus causing or mediating the inflammatory process. HC gp-39 derived peptides were predominantly recognized by autoreactive T cells from RA patients but rarely by T cells from healthy donors, thus indicating that HC gp-39 is an autoantigen in RA. The arthritogenic nature of HC gp-39 was further substantiated in the Balb/c mouse. A single, subcutaneous injection of said protein in Balb/c mice was able to initiate arthritic signs in the animals. The course of the HC gp-39- induced disease was characterized by relapses occurring periodically in fore paws

and/or hind paws and gradually developed from a mild arthritis into a more severe form. Also, a symmetrical distribution of afflicted joints was observed which is, together with the observation of recurrent relapses and nodule formation, reminiscent of disease progression in arthritis, especially RA.

Even more surprisingly it was found that administration of HC gp-39 resulted in immunological tolerance and, more importantly, in delayed and/or suppressed arthritic development.

The amino acid sequences given in SEQ ID NO's 60-78, more specifically the sequences given in SEQ ID NO's 1, 2, 5, 6, 12, 16-20, 28-30, 34, 37-39, 46-48, 53-57 resemble MHC class II restricted T cell epitopes which are present on HC gp-39. Thus, the peptides according to the invention can also be understood to encompass fragments of the autoantigen HC gp-39 which comprise one or more of the above identified MHC Class II restricted T-cell epitopes and they are also within the scope of the invention.

Although HC gp-39 was disclosed in Hakala et al., J.Biol.Chem., Vol.268, No. 34, 25803 (1993), in which it was described as a chitinase protein and suggested for use as a suitable marker for rheumatoid arthritis, any hint or suggestion towards the arthritogenic nature of HC gp-39 was absent.

The peptides according to the invention can be prepared by well known organic chemical methods for peptide synthesis such as, for example, solid-phase peptide synthesis described for instance in J. Amer. Chem. Soc. 85:2149 (1963) and Int. J. Peptide Protein Res. 35:161-214 (1990).

The peptides according to the invention can also be prepared by recombinant DNA techniques. A nucleic acid sequence coding for a peptide according to the invention or a multimer of said peptides is inserted into an expression vector. Suitable

expression vectors are, amongst others, plasmids, cosmids, virusses and YAC's (Yeast Artificial Chromosomes) which comprise the necessary control regions for replication and expression. The expression vector can be brought to expression in a host cell. Suitable host cells are, for instance, bacteria, yeast cells and mammalian cells. Such techniques are well known in the art, see for instance Sambrooke et al, Molecular Cloning: a Laboratory Manual, Cold Spring Harbor laboratory Press, Cold Spring Harbor, 1989.

The peptides according to the invention are T-cell reactive peptides, which are recognized by and are able to stimulate activated, autoreactive T-cells. These autoreactive T cells are found in the blood of RA patients but rarely in healthy donors.

Thus, according to the invention the synthetic peptides, said peptides resembling the MHC Class II restricted T-cell epitopes present on the target autoantigen HC gp-39, are very suitable for use in a therapy to induce specific T-cell tolerance to HC gp-39 in mammals, more specifically humans, suffering from T-cell mediated cartilage destruction, such as for example arthritis, more specifically rheumatoid arthritis.

Although WO 95/01995 and WO 95/02188 describe the diagnostic use of HC gp-39 as a marker for RA, the arthritogenic nature of HC gp-39 is neither disclosed nor suggested. Nowhere do they hint or suggest towards the use of fragments of HC gp-39 or T-cell reactive peptides according to the present invention in the antigen or peptide specific therapy to induce T-cell specific tolerance to the HC gp-39 in the cartilage under attack.

According to the invention, patients suffering from T-cell mediated destruction of the articular cartilage can be treated with a therapeutical composition comprising one or more peptides

according to the invention and a pharmaceutical acceptable carrier. Administration of the pharmaceutical composition according to the invention will induce systemic immunological tolerance, in particular tolerance of the specific autoreactive T cells of these patients, to the autoantigenic proteins in the articular cartilage under attack and other self antigens which display the identified MHC Class II binding T cell epitopes characterized or mimicked by the amino acid sequences of one or more of the peptides according to the invention. The induced tolerance thus will lead to a reduction of the local inflammatory response in the articular cartilage under attack.

Very suitable peptides to be used in a pharmaceutical composition according to the invention are the peptides having 16-55, preferably 16-35, more preferably 16-25, most preferably 16 amino acid residues, said peptides comprising at least one of the amino acid sequences LVCYYTWS (SEQ ID NO:60), FLCTHIIYS (SEQ ID NO:61), IIYSFANIS (SEQ ID NO:62), LKTLLSVGG (SEQ ID NO:63), FIKSVPPFL (SEQ ID NO:64), FDGLDLAWL (SEQ ID NO: 65), LYPGRRDKQ (SEQ ID NO:66), YDIAKISQH (SEQ ID NO:67), LDFISIMTY (SEQ ID NO:68), FISIMTYDF (SEQ ID NO:69), FRGOEDASP (SEQ ID NO:70), YAVGYMLRL (SEQ ID NO:71), MLRLGAPAS (SEQ ID NO:72), LAYYEICDF (SEQ ID NO:73), LRGATVHRT (SEQ ID NO:74), YLKDRQLAG (SEQ ID NO:75), LAGAMVWAL (SEQ ID NO:76), VWALDLDDF (SEQ ID NO:77) or LDLDDFQGS (SEQ ID NO:78), more in particular one of the amino acid sequences YKLVCYYTWSQYREG (SEQ ID NO:1), YTWSQYREGDGSCFP (SEQ ID NO:2), LDRFLCTHIIYSFANI (SEQ ID NO:5), THIIYSFANISNDHID (SEQ ID NO:6), PNLKTLLSVGGWNFGS (SEQ ID NO:12), NTQSRRTFIKSVPPFL (SEQ ID NO:16), TFIKSVPPFLRTHGFD (SEQ ID NO:17), PPFLRTHGFDGLDLAW (SEQ ID NO:18), HGFDGLDLAWLYPGRR (SEQ ID NO:19), DLAWLYPGRRDKQHFT (SEQ ID NO:20), TIDSSYDIAKISQHL (SEQ ID NO:28), DIAKISQHLDFISIMT (SEQ ID NO:29), QHLDISIMTYDF (SEQ ID NO:30), SPIFRGOEDASPDRES (SEQ ID NO:31).

NO:34), DYAVGYMLRLGAPASK (SEQ ID NO:37), MLRLGAPASKLVMGIP (SEQ ID NO:38), PASKLVMGIPTFGRSF (SEQ ID NO:39), GTLAYYEICDFLRGAT (SEQ ID NO:46), EICDFLRGATVHRTL (SEQ ID NO:47), RGATVHRTLGGQVPYA (SEQ ID NO:48), VKSKVQYLKDRQLAGA (SEQ ID NO:53), YLKDRQLAGAMVWALD (SEQ ID NO:54), LAGAMVWALDLDDFQG (SEQ ID NO:55), WALDLDDFQGSFCGQD (SEQ ID NO:56) or DFQGSFCGQDLRFPLT (SEQ ID NO:57).

Specifically preferred in a pharmaceutical composition according to the invention are the peptides having 16-55, preferably 16-35, more preferably 16-25, most preferably 16 amino acid residues, said peptides comprising at least one of the amino acid sequences YKLVCYYTSWSQYREG (SEQ ID NO:1), YTSWSQYREGDGSCFP (SEQ ID NO:2), LDRFLCTHIIYSFANI (SEQ ID NO:5), THIIYSFANISNDHID (SEQ ID NO:6), PNLKTLLSVGGWNFGS (SEQ ID NO:12), QHLDFISIMTYDFHGA (SEQ ID NO:30), SPLFRGQEDASPDRFS (SEQ ID NO:34), DYAVGYMLRLGAPASK (SEQ ID NO:37), MLRLGAPASKLVMGIP (SEQ ID NO:38), YLKDRQLAGAMVWALD (SEQ ID NO:54) or LAGAMVWALDLDDFQG (SEQ ID NO:55).

Highly preferred in a pharmaceutical composition according to the invention are peptides having 16-55, preferably 16-35, more preferably 16-25, most preferably 16 amino acid residues, said peptides comprising at least one of the amino acid sequences YTSWSQYREGDGSCFP (SEQ ID NO:2), SPLFRGQEDASPDRFS (SEQ ID NO:34), MLRLGAPASKLVMGIP (SEQ ID NO:38), YLKDRQLAGAMVWALD (SEQ ID NO:54) or LAGAMVWALDLDDFQG (SEQ ID NO:55).

Most preferred in a pharmaceutical composition according to the invention are hexadecapeptides consisting of the amino acid sequence YKLVCYYTSWSQYREG (SEQ ID NO:1) YTSWSQYREGDGSCFP (SEQ ID NO:2), LDRFLCTHIIYSFANI (SEQ ID NO:5), THIIYSFANISNDHID (SEQ ID NO:6), PNLKTLLSVGGWNFGS (SEQ ID NO:12), QHLDFISIMTYDFHGA (SEQ ID NO:30), SPLFRGQEDASPDRFS (SEQ ID NO:34), DYAVGYMLRLGAPASK (SEQ ID NO:37), MLRLGAPASKLVMGIP (SEQ ID NO:38), YLKDRQLAGAMVWALD

(SEQ ID NO:54) or LAGAMVWALDLDDFQG (SEQ ID NO:55), more in particular the amino acid sequences YTSWSQYREGDGSCFP (SEQ ID NO:2), SPLFRGQEDASPD RFS (SEQ ID NO:34), MLRLGAPASKLVMGIP (SEQ ID NO:38), YLKDRQLAGAMVWALD (SEQ ID NO:54) or LAGAMVWALDLDDFQG (SEQ ID NO:55).

The peptides according to the invention have the advantage that they have a specific effect on the autoreactive T cells thus leaving the other components of the immune system intact as compared to the nonspecific suppressive effect of immunosuppressive drugs. Treatment with the peptides according to the invention will be safe and no toxic side effects will occur.

Systemic immunological tolerance can be attained by administering high or low doses of peptides according to the invention. The amount of peptide will depend on the route of administration, the time of administration, the age of the patient as well as general health conditions and diet.

In general, a dosage of 0.01 to 1000  $\mu$ g of peptide per kg body weight, preferably 0.5 to 500  $\mu$ g, more preferably 0.1 to 100  $\mu$ g of peptide can be used.

Pharmaceutical acceptable carriers are well known to those skilled in the art and include, for example, sterile saline, lactose, sucrose, calcium phosphate, gelatin, dextrin, agar, pectin, peanut oil, olive oil, sesame oil and water. Other carriers may be, for example MHC class II molecules, if desired embedded in liposomes.

In addition the pharmaceutical composition according to the invention may comprise one or more adjuvants. Suitable adjuvants include, amongst others, aluminium hydroxide, aluminium phosphate, amphigen, tocophenols, monophosphenyl lipid A, muramyl dipeptide and saponins such as Quill A. Preferably, the

adjuvants to be used in the tolerance therapy according to the invention are mucosal adjuvants such as the cholera toxine B-subunit or carbomers, which bind to the mucosal epithelium. The amount of adjuvant depends on the nature of the adjuvant itself.

5 Furthermore the pharmaceutical composition according to the invention may comprise one or more stabilizers such as, for example, carbohydrates including sorbitol, mannitol, starch, sucrodedextrin and glucose, proteins such as albumin or casein, and buffers like alkaline phosphates.

10 Suitable administration routes are intramuscular injections, subcutaneous injections, intravenous injections or intraperitoneal injections, oral administration and nasal sprays.

15 The peptides according to the invention are also very suitable for use in a diagnostic method to detect the presence of activated autoreactive T cells involved in the chronic inflammation and destruction of the articular cartilage.

20 The diagnostic method according to the invention comprises the following steps:

- a) isolation of the peripheral blood mononuclear cells (PBMC) from a blood sample of an individual,
- b) culture said PBMC under suitable conditions,
- c) incubation of said PBMC culture in the presence of one or  
25 more peptides according to the invention, and
- d) detection of a response of T cells, for example a proliferative response, indicating the presence of activated autoreactive T cells in the individual.

30 The detection of a proliferative response of T cells can be detected by, for example, the incorporation of  $^3\text{H}$ -thymidine.

Also within the scope of the invention are test kits which comprise one or more peptides according to the invention. These

test kits are suitable for use in a diagnostic method according to the invention.

The following examples are illustrative for the invention and should in no way be interpreted as limiting the scope of the invention.

## EXAMPLES

### METHODS

#### Patients

This study included 7 DR4(DRB1\*0401)-positive patients diagnosed as suffering from RA according to the ARA criteria (Arnett et al., (1988), Arthritis Rheum. 31, 315). Peripheral blood samples were obtained with informed consent. There were five women and two men aged 46-79 years. Their duration of disease ranged from over 10 to over 30 years. Three out of 7 patients had at least 3 swollen joints. Four patients did not show any signs of active disease. All patients were on medication: Four patients were treated with prednisone, three patients received anti-rheumatic agents and 4 patients were treated with NSAID's as well.

Peripheral blood samples from 5 healthy donors carrying the DR4(DRB1\*0401) specificity were obtained with informed consent and included in this study as a control.

#### Definition of HLA-DR polymorphisms

Patient and healthy donor peripheral blood mononuclear cells (PBMC) isolated from heparinized peripheral blood by standard centrifugation on Ficoll-Paque were stimulated with PHA (Wellcome, Dartford, UK) to obtain  $5 \times 10^6$ - $10^7$  lymphocytes. The

QIA amp blood kit (QIAGEN Inc, ) was used to purify chromosomal DNA from cultured cells according to the manufacturers instructions. Chromosomal DNA extracts were analysed using a DR 'low resolution' SSP kit. DR4 subtyping was performed using the  
 5 Dynal DRB1\*04-SSP kit. MHC DR typing was performed at the Transplant Serology Laboratory, University Hospital, Nijmegen, The Netherlands.

Table I

RA Patient	stage	synovitis	duration	HLA-DR
191	IV	no	>30 years	0401/01
259	III-IV	yes	>30 years	0401/16
262	III-IV	yes	>10 years	0401/0408
272	III-IV	no	> 30 years	0401/0701
276	IV	no	>30 years	0401/14
286	IV	no	20 years	0401/0408
287	III-IV	yes	20 years	0401/13
HD				HLA-DR
155				0401/14
157				0401/13
168				0401/07
230				0401/07
235				0401/13

### Peptide synthesis

Peptides were synthesized at Eurosequence (Groningen, The  
 15 Netherlands). Peptides were synthesized from the C-terminus to the N-terminus on a 10 µmol scale using solid-phase Fmoc

chemistry. The crude peptides were partly purified by several other preparations. As indicated by the manufacturer, at least 35% of the lyophilized product contained the desired full length product. The rest contained salt and remaining solvent. The quality of the final product was checked by sequence analysis, amino acid analysis and/or RF-HPLC. The sequences of the peptides synthesized are enlisted in Table II.

Table II: Amino acid sequences of the peptides used in this study.

SEQ ID NO:	residu	peptide
1	22-37	YKLVCYYTSWSQYREG
2	28-43	YTSWSQYREGDGSCFP
3	34-49	YREGDGSCFPDALDRF
4	40-55	SCFPDALDRFLCTHII
5	46-61	LDRFLCTHIIYSFANI
6	52-67	THIIYSFANISNDHID
7	58-73	FANISNDHIDTWEWND
8	64-79	DHIDTWEWNDVTLYGM
9	70-85	EWNDVTLYGMLNTLKN
10	76-91	LYGMLNTLKNRNPNLK
11	82-97	TLKNRNPNLKTLLSVG
12	88-103	PNLKTLLSVGGWNFGS
13	94-109	LSVGGWNFGSQRFSKI
14	100-115	NFGSQRFSKIASNTQS
15	106-121	FSKIASNTQSRRTFIK
16	112-127	NTQSRRTFIKSVPPFL
17	118-133	TFIKSVPPFLRTHGFD
18	124-139	PPFLRTHGFDGLDLAW
19	130-145	HGFDGLDLAWLYPGRR

20	136-151	DLAWLYPGRRDKQHFT
21	142-157	PGRRDQHFHTTLIKEM
22	148-163	QHFTTLIKEMKAEFIK
23	154-169	IKEMKAEFIKEAQPGK
24	160-175	EFIKEAQPGKKQLLLS
25	166-181	QPGKKQLLLSAALSAG
26	172-187	LLLSAALSAGKVTIDS
27	178-193	LSAGKVTIDSSYDIAC
28	184-199	TIDSSYDIAKISQHLD
29	190-205	DIAKISQHLD FISIMT
30	196-211	QHLD FISIMTYDFHGA
31	202-217	SIMTYDFHGAWRGTTG
32	208-223	FHGAWRGTTGHHSPLF
33	214-229	GTTGHHSPLFRGQEDA
34	220-235	SPLFRGQEDASPD RFS
35	226-241	QEDASPD RFSNTDYAV
36	232-247	DRFSNTDYAVGYMLRL
37	238-253	DYAVGYMLRLGAPASK
38	244-259	MLRLGAPASKLVMGIP
39	250-265	PASKLVMGIPTFGRSF
40	256-271	MGIPTFGRSFTLASSE
41	262-277	GRSFTLASSETGVGAP
42	268-283	ASSETGVGAPISGPGI
43	274-289	VGAPISGPGIPGRFTK
44	280-295	GPGIPGRFTKEAGTLA
45	286-301	RFTKEAGTLAYYEICD
46	292-307	GTLAYYEICDFLRGAT
47	298-313	EICDFLRGATVHRTL G
48	304-319	RGATVHRTL GQQVPYA
49	310-325	RTL GQQVPYATKGNQW
50	316-331	VPYATKGNQWVGYYDDQ

51	322-337	GNQWVGYYDDQESVKSK
52	328-343	YDDQESVKSKVQYLKD
53	334-349	VKSKVQYLKDRQLAGA
54	340-355	YLKDRQLAGAMVWALD
55	346-361	LAGAMVWALDLDDFQG
56	352-377	WALDLDDFQGSFCGQD
57	358-373	DFQGSFCGQDLRFPLT
58	364-379	CGQDLRFPLTNAIKDA
59	368-383	LRFPLTNAIKDALAAT

#### Peptide HLA-DR binding assay

DR4 (DRB1\*0401) and DR4 (DRB1\*0404) molecules were purified from the homozygous EBV-transformed human B lymphoblastoid cell lines Huly138IC2 and BM92 using the mAb L243, directed against a monomorphic determinant on the DR-complex (Lampson, L.A. and R. Levy (1980), J. Immunol. 125:293-299).

The peptide binding studies were performed using a semi-quantitative competition binding assay (Joosten et al 1994, Int. Immunol. 6, 751). Briefly, purified HLA-DR molecules (30 nM DR4 (DRB1\*0401) or 15 nM DR4 (DRB1\*0404) were incubated at pH5.0 with 50 nM biotinylated marker peptide (HA 309<sub>Y→F</sub>) and a concentration range of competitor peptide in a final volume of 25  $\mu$ l binding buffer (PBS containing 0.01% NaN<sub>3</sub>, 0.05% NP-40, 5% DMSO, 1 mM AEBSF, 1 mM N-ethyl maleimide, 8 mM EDTA and 10  $\mu$ M pepstatin A). After 44 hr of incubation at RT, HLA-DR-bound marker peptide was separated from free marker peptide using a 96 well vacuum dotblot apparatus (Hybri.dot, BRL) and a nitrocellulose membrane (Hybond ECL, Amersham, UK). The nitrocellulose filters were blocked with 0.5% DNA blocking reagent (Boehringer) in 0.1 M maleic acid, 150 mM NaCl, pH7.5.

After 0.5-1 hr, the filters were washed in PBS, 0.05% Tween 20 (Sigma) and incubated with Streptavidin-HRPO (Southern Biotechnology) in a 1:10.000 dilution. Biotinylated peptides were detected by enhanced chemiluminescence using a Western Blot ECL kit (Amersham). Exposure of the preflashed films (Hyperfilm-ECL, Amersham) was for 10 min. The spots were analysed by scanning the films and using Image Quant/Excel software for analysis.

The affinity of a given peptide for binding DRB1\*0401-encoded molecules was related to competition with the marker peptide. This relative binding affinity was defined as the peptide concentration at which the signal was reduced to 50% (IC<sub>50</sub>).

#### **Proliferative responses of blood mononuclear cells**

In order to identify T-cell epitopes within HC gp-39, 59 peptides of 16 AA in length, overlapping by 10 AA were tested for their capacity to induce a proliferative response in PBMC from RA patients and healthy controls carrying the DR4 (DRB1\*0401) specificity (Table 1). Table 2 enlists the sequences of the peptides tested.

PBMC obtained from heparinized venous peripheral blood were isolated by standard centrifugation on a Ficoll-Paque gradient. Cells were cultured in four-fold at a concentration of  $1,5 \times 10^5$  cells / well in medium supplemented with 10% heat-inactivated, autologous plasma, L-glutamine, 2-ME and antibiotics in flatbottomed microtiter plates. Cells were incubated in medium alone or in the presence of phytohaemagglutinin (PHA) (2.5 µg/ml) to assert cell viability, or in the presence of 10 or 100 µg/ml of the HC gp-39-derived peptides. In several cases, sets of 2 or 3 sequential peptides were tested due to limited PBMC numbers of individual donors. Cultures were incubated in a total

volume of 210  $\mu$ l for 7 days at 37 °C in a humidified atmosphere of 5% CO<sub>2</sub>. Cultures were pulsed during the last 18 hours with 0.25  $\mu$ Ci <sup>3</sup>H-thymidine ([<sup>3</sup>H]TdR). Cells were harvested on glassfiber filters and [<sup>3</sup>H]TdR incorporation was measured by gas scintillation (Packard Matrix 96  $\beta$ counter). Only peptides inducing a proliferative response at both 10 and 100  $\mu$ g/ml were considered to contain a T-cell epitope. Responses were defined positive if stimulation index values (SI, antigen-specific counts per 5min (cp5m)/ background cp5m) exceeded or equaled 2.

## RESULTS

### Identification of T-cell epitopes by proliferative responses of blood mononuclear cells

T-cell reactivity to HC gp-39-derived peptides was analyzed by measuring the PBMC proliferative response in DR4 (DRB1\*0401)-positive RA patients and healthy donors. Proliferative responses were tested in autologous plasma. In Table IIIA and IIIE the results of 7 experiments are presented showing the responses of RA patients (Table IIIA) and the responses of healthy donors (Table IIIB) to 59 overlapping sequences derived from HC gp-39. Donors found to respond to both concentrations (100 and 10  $\mu$ g/ml) of a peptide were ranked as responders and donors which did not respond to both concentrations tested were ranked as non-responders (NR).

Responses to the individual peptides 1, 2, 5, 6, 12, 15, 30, 34, 37, 38, 40, 41, 54 and 55 (the numbers respond to the respective SEQ ID NO of each peptide, for example, peptide 30 means: peptide having amino acid sequence of SEQ ID NO:30) were

observed in one or more donors, thereby identifying these sequences as T-cell epitopes.

Interestingly, responses to peptides 2, 34, 38, 40, 54 and 55 were observed in RA patients only.

5 On the other hand, peptides 12 and 41 induced only responses in healthy donors (230, 235) thus far.

In addition, as can be seen in Table 3, responses were found to the following sets of: peptides 1/2, 1/2/3, 4/5/6, 5/6, 15/16, 17/18, 19/20, 28/29/30, 29/30, 37/38, 37/38/39, 39/40, 10 46/47/48, 53/54, 55/56 and 55/56/57. These results are in accordance with most of the results of the individual peptides mentioned above. Moreover, the responses against the sets of peptides define regions that contain additional T-cell epitopes, i.e. the regions covered by peptides 16-20 (residu 112-151), 28-15 29 (residu 184-205), 38-40 (residu 244-271), 46-48 (residu 292-319) and 53-57 (334-373).

Six out of 7 DR4 (DRB1\*0401)-positive RA patients responded to HC gp-39-derived peptides or sets of peptides and were 20 therefore ranked as responders. In the healthy donor group (HD), 3 out of 5 donors were ranked as responders. In general, RA patients appeared to respond to many more HC gp-39 regions than healthy donors (healthy donor 230 being an exception). For example, PBMC from RA patient 272, which were tested against 25 individual peptides, appeared to respond to a total of 11 peptides (1, 2, 5, 6, 30, 34, 37, 38, 40, 54 and 55). PBMC of the other patients (patient 287 being an exception) showed responses against sets of peptides overlapping these 11 sequences and identified some additional regions containing T-30 cell epitopes (peptides 14-20 and 46-48).

PBMC derived from a healthy donor (230) further confirmed the presence of T-cell epitopes in peptides 1, 5, 6, 15, 30 and 37.

Overall, the peptides or sets of peptides most frequently  
5 recognized contain peptides 1/2, 5/6, 30, 37/38, 54/55).

#### Correlation of T-cell epitopes and DRB4 (DRB1\*0401) binding

Peptides 1, 2, 5, 6, 12, 15, 30, 34, 37, 38, 40, 41, 54 and 55 were all found to stimulate peripheral blood derived T-cells. As a corollary to this finding, all of these peptides were found to bind to DR4 (DRB1\*0401) with relatively high affinity (except peptides 2 and 38 which bind with intermediate relative affinity). Peptides 3, 4, 16, 17, 18, 19, 20, 28, 29, 39, 46, 47, 48, 53, 56 and 57 were tested in sets rather than  
15 individually. It is very likely that several of these peptides also contain relevant T-cell epitopes. In any case, these peptides all can bind DRB4 (DRB1\*0401) with high to intermediate relative affinity (except for peptide 20 which binds with poor relative affinity).

20

Table IIIA: Peptide-induced proliferative responses of PBMC from RA patients.

RA:	272	262	276	286	191	287	259	0401
peptide	0401	0401	0401	0401	0401	0401	0401	binding
	R	R	R	R	R	NR	R	
1	pos							+++
2	pos		pos	pos	pos		pos	+
3								+
4								+
5	pos						pos	+++
6	pos		pos	pos				+++
7								

8								
9								
10								
11								
12								
13								
14&								
15&								+++
16				pos				+++
17								++
18			pos					+
19								+
20				pos				+/-
21								
22								
23								
24								
25								
26								
27								
28								+++
29						pos		+++
30	pos	pos	pos	pos				+++
31								
32								
33								
34	pos							+++
35								
36								
37	pos							+++
38	pos	pos	pos	pos		pos		+
39								++
40&	pos			pos				+++
41&								

42								
43								
44								
45								
46					pos			+++
47								+++
48								+
49								
50								
51&								
52&								
53								+++
54	pos		pos	pos				+++
55	pos							+++
56				pos	pos			+++
57								++
58								
59								
BG	0.2	0.7	0.5	0.8	2.4	0.9	0.2	

pos = positive responses to both 100 and 10 microgram/ml of peptide or sets of peptides ( $SI \geq 2$  were regarded positive). Together the peptides (16 AA in length and overlapping by 10

5 AA) cover the complete mature sequence of mature HC gp-39 (residu 22-383). Peptides were synthesized at Eurosequence (Groningen, The Netherlands). RA = rheumatoid arthritis patient. 0401 = donor carrying the RA-associated HLA-DRB1\*0401 specificity. NR = non-responder. R = responder. BG = mean of

10 background counts per 5 minutes  $\times 10^{-3}$  measured in wells without antigen. +++ = high affinity binder ( $IC_{50} < 1 \mu M$ ); ++ = good affinity binder ( $1 < IC_{50} < 10 \mu M$ ); + = intermediate binder ( $10 < IC_{50} < 100 \mu M$ ); +/- = poor binder ( $100 < IC_{50} < 1000 \mu M$ ); - = non-binder ( $IC_{50} > 1000 \mu M$ )

Table IIIB: Peptide-induced proliferative responses of PBMC  
from healthy donors.

5

HD	155	157	168	230	235	0401
peptide	0401	0401	0401	0401	0401	binding
	R	NR	NR	R	R	
1				pos		+++
2						
3						
4						
5				pos		+++
6				pos		+++
7						
8						
9						
10						
11						
12				pos		+++
13						
14&						
15&				pos		+++
16						
17						
18						
19						
20						
21						
22						
23						
24						

25						
26						
27						
28						
29						
30				pos		+++
31						
32						
33						
34						
35						
36						
37	pos			pos	pos	+++
38						
39						
40						
41					pos	+++
42						
43						
44						
45						
46						
47						
48						
49						
50						
51						
52						
53						
54						
55						

56						
57						
58						
59						
BG	4,2	10,4	2,2	3,6	3,5	

pos = positive responses to both 100 and 10 microgram/ml of peptide or sets of peptides ( $SI \geq 2$  were regarded positive). Together the peptides (16 AA in length and overlapping by 10 AA) cover the complete mature sequence of mature HC gp-39 (residu 22-383). Peptides were synthesized at Eurosequence (Groningen, The Netherlands). HD = healthy donor. 0401 = donor carrying the RA-associated HLA-DRB1\*0401 specificity. NR = non-responder. R = responder. BG = mean of background counts per 5 minutes  $\times 10^{-3}$  measured in wells without antigen. +++ = high affinity binder ( $IC_{50} < 1 \mu M$ ); ++ = good affinity binder ( $1 < IC_{50} < 10 \mu M$ ); + = intermediate binder ( $10 < IC_{50} < 100 \mu M$ ); +/- = poor binder ( $100 < IC_{50} < 1000 \mu M$ ); - = non-binder ( $IC_{50} > 1000 \mu M$ )

## 15 ABBREVIATIONS

AEBSF: 4-(2-AminoEthyl)-BenzeneSulfonyl Fluoride

BB: binding buffer

BCA: Bicinchoninic Acid

BSA: bovine serum albumin

20 DMSO: Dimethyl Sulfoxide

ECL: Enhanced Chemiluminescence

EDTA: EthyleneDiamine Tetra Acetic acid

FACS: Fluorescence Activated Cell Sorter

HLA: Human Leukocyte Antigens

25 HPLC: High Pressure Liquid Chromatography

HRP: Horse Radish Peroxidase

MHC CLASS II: Major Histocompatibility Complex class II

NMR: Nuclear Magnetic Resonance  
NP-40: Nonidet P-40  
PBS: Phosphate Buffered Saline  
PVDF: Polyvinylidene difluoride  
5 RA: Rheumatoid Arthritis  
SDS-PAGE: Sodium DodecylSulfate Polyacrylamide Gel  
Electrophoresis

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

5

## (i) APPLICANT:

- (A) NAME: Akzo Nobel N.V.  
(B) STREET: Velperweg 76  
(C) CITY: Arnhem  
(E) COUNTRY: The Netherlands  
(F) POSTAL CODE (ZIP): 6824 BM  
(G) TELEPHONE: 0421-666376  
(H) TELEFAX: 0412-650592  
(I) TELEX: 37503 akpha nl

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(ii) TITLE OF INVENTION: Novel Peptides Suitable For Use In  
Antigen Specific Immunosuppressive Therapy

(iii) NUMBER OF SEQUENCES: 78

20

## (iv) COMPUTER READABLE FORM:

- (A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

25

(EPO)

## (2) INFORMATION FOR SEQ ID NO: 1:

30

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids

29

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Tyr Lys Leu Val Cys Tyr Tyr Thr Ser Trp Ser Gln Tyr Arg Glu Gly  
1 5 10 15

15

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

20

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: peptide

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Tyr Thr Ser Trp Ser Gln Tyr Arg Glu Gly Asp Gly Ser Cys Phe Pro  
1 5 10 15

## (2) INFORMATION FOR SEQ ID NO: 3:

- 5 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 16 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: peptide

## 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Tyr Arg Glu Gly Asp Gly Ser Cys Phe Pro Asp Ala Leu Asp Arg Phe  
1 5 10 15

20

## (2) INFORMATION FOR SEQ ID NO: 4:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 16 amino acids
  - 25 (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

30

31

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Ser Cys Phe Pro Asp Ala Leu Asp Arg Phe Leu Cys Thr His Ile Ile  
1 5 10 15

5

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: peptide

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

20

Leu Asp Arg Phe Leu Cys Thr His Ile Ile Tyr Ser Phe Ala Asn Ile  
1 5 10 15

25 (2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

30

32

(ii) MOLECULE TYPE: peptide

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Thr His Ile Ile Tyr Ser Phe Ala Asn Ile Ser Asn Asp His Ile Asp  
1 5 10 15

10 (2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: peptide

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

25 Phe Ala Asn Ile Ser Asn Asp His Ile Asp Thr Trp Glu Trp Asn Asp  
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 8:

30

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

33

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

10 Asp His Ile Asp Thr Trp Glu Trp Asn Asp Val Thr Leu Tyr Gly Met  
1 5 10 15

15 (2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- 20 (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Glu Trp Asn Asp Val Thr Leu Tyr Gly Met Leu Asn Thr Leu Lys Asn  
30 1 5 10 15

## (2) INFORMATION FOR SEQ ID NO: 10:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Leu Tyr Gly Met Leu Asn Thr Leu Lys Asn Arg Asn Pro Asn Leu Lys  
1 5 10 15

## (2) INFORMATION FOR SEQ ID NO: 11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

35

Thr Leu Lys Asn Arg Asn Pro Asn Leu Lys Thr Leu Leu Ser Val Gly  
1 5 10 15

## 5 (2) INFORMATION FOR SEQ ID NO: 12:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Pro Asn Leu Lys Thr Leu Leu Ser Val Gly Gly Trp Asn Phe Gly Ser  
20 1 5 10 15

## (2) INFORMATION FOR SEQ ID NO: 13:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Leu Ser Val Gly Gly Trp Asn Phe Gly Ser Gln Arg Phe Ser Lys Ile

1

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(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

10

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

20

Asn Phe Gly Ser Gln Arg Phe Ser Lys Ile Ala Ser Asn Thr Gln Ser

1

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25 (2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

30

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

37

(ii) MOLECULE TYPE: peptide

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Phe Ser Lys Ile Ala Ser Asn Thr Gln Ser Arg Arg Thr Phe Ile Lys  
1 5 10 15

10 (2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: peptide

20

(v) FRAGMENT TYPE: internal

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Asn Thr Gln Ser Arg Arg Thr Phe Ile Lys Ser Val Pro Pro Phe Leu  
1 5 10 15

30

(2) INFORMATION FOR SEQ ID NO: 17:

38

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

15 Thr Phe Ile Lys Ser Val Pro Pro Phe Leu Arg Thr His Gly Phe Asp  
1 5 10 15

## (2) INFORMATION FOR SEQ ID NO: 18:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

39

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Pro Pro Phe Leu Arg Thr His Gly Phe Asp Gly Leu Asp Leu Ala Trp  
1 5 10 15

5

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:

10

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

His Gly Phe Asp Gly Leu Asp Leu Ala Trp Leu Tyr Pro Gly Arg Arg  
1 5 10 15

25

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:

30

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

40

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

10

Asp Leu Ala Trp Leu Tyr Pro Gly Arg Arg Asp Lys Gln His Phe Thr  
1 5 10 15

15 (2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

25 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

30

Pro Gly Arg Arg Asp Lys Gln His Phe Thr Thr Leu Ile Lys Glu Met  
1 5 10 15

41

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Gln His Phe Thr Thr Leu Ile Lys Glu Met Lys Ala Glu Phe Ile Lys  
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

42

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Ile Lys Glu Met Lys Ala Glu Phe Ile Lys Glu Ala Gln Pro Gly Lys  
1                      5                      10                      15

5

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Glu Phe Ile Lys Glu Ala Gln Pro Gly Lys Lys Gln Leu Leu Leu Ser  
1                      5                      10                      15

25

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single

30

43

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

10

Gln Pro Gly Lys Lys Gln Leu Leu Leu Ser Ala Ala Leu Ser Ala Gly

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15 (2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

25 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

30

Leu Leu Leu Ser Ala Ala Leu Ser Ala Gly Lys Val Thr Ile Asp Ser

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## (2) INFORMATION FOR SEQ ID NO: 27:

## (i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Leu Ser Ala Gly Lys Val Thr Ile Asp Ser Ser Tyr Asp Ile Ala Lys  
1 5 10 15

## (2) INFORMATION FOR SEQ ID NO: 28:

## (i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

45

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Thr Ile Asp Ser Ser Tyr Asp Ile Ala Lys Ile Ser Gln His Leu Asp

1

5

10

15

5

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

Asp Ile Ala Lys Ile Ser Gln His Leu Asp Phe Ile Ser Ile Met Thr

1

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25

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

30

46

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

10

Gln His Leu Asp Phe Ile Ser Ile Met Thr Tyr Asp Phe His Gly Ala

1

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15 (2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

25 (v) FRAGMENT TYPE: internal

30

Ser Ile Met Thr Tyr Asp Phe His Gly Ala Trp Arg Gly Thr Thr Gly

1

5

10

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47

## (2) INFORMATION FOR SEQ ID NO: 32:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

Phe His Gly Ala Trp Arg Gly Thr Thr Gly His His Ser Pro Leu Phe  
1 5 10 15

## (2) INFORMATION FOR SEQ ID NO: 33:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

Gly Thr Thr Gly His His Ser Pro Leu Phe Arg Gly Gln Glu Asp Ala

1

5

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(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Ser Pro Leu Phe Arg Gly Gln Glu Asp Ala Ser Pro Asp Arg Phe Ser

1

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(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

30

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

10  
Gln Glu Asp Ala Ser Pro Asp Arg Phe Ser Asn Thr Asp Tyr Ala Val  
1 5 10 15

15 (2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

25 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

30  
Asp Arg Phe Ser Asn Thr Asp Tyr Ala Val Gly Tyr Met Leu Arg Leu  
1 5 10 15

50

## (2) INFORMATION FOR SEQ ID NO: 37:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

Asp Tyr Ala Val Gly Tyr Met Leu Arg Leu Gly Ala Pro Ala Ser Lys  
1 5 10 15

## (2) INFORMATION FOR SEQ ID NO: 38:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

51

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

Met Leu Arg Leu Gly Ala Pro Ala Ser Lys Leu Val Met Gly Ile Pro

1

5

10

15

5

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

Pro Ala Ser Lys Leu Val Met Gly Ile Pro Thr Phe Gly Arg Ser Phe

1

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25

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

30

52

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

10  
Met Gly Ile Pro Thr Phe Gly Arg Ser Phe Thr Leu Ala Ser Ser Glu  
1 5 10 15

15 (2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

25 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

30  
Gly Arg Ser Phe Thr Leu Ala Ser Ser Glu Thr Gly Val Gly Ala Pro  
1 5 10 15

## (2) INFORMATION FOR SEQ ID NO: 42:

## (i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## 10 (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

## 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

Ala Ser Ser Glu Thr Gly Val Gly Ala Pro Ile Ser Gly Pro Gly Ile

1 5 10 15

## 20 (2) INFORMATION FOR SEQ ID NO: 43:

## (i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## 30 (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

54

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

Val Gly Ala Pro Ile Ser Gly Pro Gly Ile Pro Gly Arg Phe Thr Lys  
1 5 10 15

5

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

10

15

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

Gly Pro Gly Ile Pro Gly Arg Phe Thr Lys Glu Ala Gly Thr Leu Ala  
1 5 10 15

25

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single

30

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

10

Arg Phe Thr Lys Glu Ala Gly Thr Leu Ala Tyr Tyr Glu Ile Cys Asp  
1 5 10 15

15 (2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

25 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

30

Gly Thr Leu Ala Tyr Tyr Glu Ile Cys Asp Phe Leu Arg Gly Ala Thr  
1 5 10 15

## (2) INFORMATION FOR SEQ ID NO: 47:

## (i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

Glu Ile Cys Asp Phe Leu Arg Gly Ala Thr Val His Arg Thr Leu Gly  
1 5 10 15

## (2) INFORMATION FOR SEQ ID NO: 48:

## (i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

Arg Gly Ala Thr Val His Arg Thr Leu Gly Gln Gln Val Pro Tyr Ala

5 1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 49:

10 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

Arg Thr Leu Gly Gln Gln Val Pro Tyr Ala Thr Lys Gly Asn Gln Trp

25 1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 50:

30 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

58

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5

(v) FRAGMENT TYPE: internal

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Val Pro Tyr Ala Thr Lys Gly Asn Gln Trp Val Gly Tyr Asp Asp Gln

1

5

10

15

15

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

20

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

25

(v) FRAGMENT TYPE: internal

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

Gly Asn Gln Trp Val Gly Tyr Asp Asp Gln Glu Ser Val Lys Ser Lys  
1 5 10 15

5 (2) INFORMATION FOR SEQ ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

Tyr Asp Asp Gln Glu Ser Val Lys Ser Lys Val Gln Tyr Leu Lys Asp  
1 5 10 15

25 (2) INFORMATION FOR SEQ ID NO: 53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

60

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

Val Lys Ser Lys Val Gln Tyr Leu Lys Asp Arg Gln Leu Ala Gly Ala

10 1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 54:

15 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

Tyr Leu Lys Asp Arg Gln Leu Ala Gly Ala Met Val Trp Ala Leu Asp

30 1 5 10 15

61

(2) INFORMATION FOR SEQ ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

Leu Ala Gly Ala Met Val Trp Ala Leu Asp Leu Asp Asp Phe Gln Gly  
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

62

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

Trp Ala Leu Asp Leu Asp Asp Phe Gln Gly Ser Phe Cys Gly Gln Asp  
1 5 10 15

5

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

10

15

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

Asp Phe Gln Gly Ser Phe Cys Gly Gln Asp Leu Arg Phe Pro Leu Thr  
1 5 10 15

25

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single

30

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

10

Cys Gly Gln Asp Leu Arg Phe Pro Leu Thr Asn Ala Ile Lys Asp Ala  
1 5 10 15

15 (2) INFORMATION FOR SEQ ID NO: 59:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

25 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

30

Leu Arg Phe Pro Leu Thr Asn Ala Ile Lys Asp Ala Leu Ala Ala Thr  
1 5 10 15

## (2) INFORMATION FOR SEQ ID NO: 60:

## (i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 9 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## 10 (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

## 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

Leu Val Cys Tyr Tyr Thr Ser Trp Ser

1 5

20

## (2) INFORMATION FOR SEQ ID NO: 61:

## (i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 9 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## 30 (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

65

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

Phe Leu Cys Thr His Ile Ile Tyr Ser

1

5

5

(2) INFORMATION FOR SEQ ID NO: 62:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

Ile Ile Tyr Ser Phe Ala Asn Ile Ser

1

5

(2) INFORMATION FOR SEQ ID NO: 63:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

66

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

10

Leu Lys Thr Leu Leu Ser Val Gly Gly

1

5

15 (2) INFORMATION FOR SEQ ID NO: 64:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

25 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

30

Phe Ile Lys Ser Val Pro Pro Phe Leu

1

5

## (2) INFORMATION FOR SEQ ID NO: 65:

## (i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 9 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## 10 (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

## 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

Phe Asp Gly Leu Asp Leu Ala Trp Leu

1

5

20

## (2) INFORMATION FOR SEQ ID NO: 66:

## (i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 9 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## 30 (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

5

Leu Tyr Pro Gly Arg Arg Asp Lys Gln

1

5

10 (2) INFORMATION FOR SEQ ID NO: 67:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

15

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

20

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

25

Tyr Asp Ile Ala Lys Ile Ser Gln His

1

5

30 (2) INFORMATION FOR SEQ ID NO: 68:

(i) SEQUENCE CHARACTERISTICS:

69

- (A) LENGTH: 9 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

Leu Asp Phe Ile Ser Ile Met Thr Tyr

15

1

5

(2) INFORMATION FOR SEQ ID NO: 69:

20

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 9 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

30

70

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

Phe Ile Ser Ile Met Thr Tyr Asp Phe

1 5

5

(2) INFORMATION FOR SEQ ID NO: 70:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 9 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

Phe Arg Gly Gln Glu Asp Ala Ser Pro

1 5

25

(2) INFORMATION FOR SEQ ID NO: 71:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 9 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single

71

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

10

Tyr Ala Val Gly Tyr Met Leu Arg Leu

1

5

15 (2) INFORMATION FOR SEQ ID NO: 72:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

25 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

30

Met Leu Arg Leu Gly Ala Pro Ala Ser

1

5

## (2) INFORMATION FOR SEQ ID NO: 73:

## (i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 9 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## 10 (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

## 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

Leu Ala Tyr Tyr Glu Ile Cys Asp Phe

1 5

20

## (2) INFORMATION FOR SEQ ID NO: 74:

## (i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 9 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## 30 (ii) MOLECULE TYPE: peptide

## (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

5

Leu Arg Gly Ala Thr Val His Arg Thr

1

5

10 (2) INFORMATION FOR SEQ ID NO: 75:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

15 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

20 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

25

Tyr Leu Lys Asp Arg Gln Leu Ala Gly

1

5

30 (2) INFORMATION FOR SEQ ID NO: 76:

(i) SEQUENCE CHARACTERISTICS:

74

- (A) LENGTH: 9 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

5

- ```
(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal
```

10

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

Leu Ala Gly Ala Met Val Trp Ala Leu

15      1                          5

- (2) INFORMATION FOR SEQ ID NO: 77:

20 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 9 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

25

- (ii) MOLECULE TYPE: peptide
- (v) FRAGMENT TYPE: internal

30

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

Val Trp Ala Leu Asp Leu Asp Asp Phe

1

5

5

(2) INFORMATION FOR SEQ ID NO: 78:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

Leu Asp Leu Asp Asp Phe Gln Gly Ser

1

5

CLAIMS

1. Peptides consisting of 16 to 55 amino acid residues, said peptide comprising at least one of the amino acid sequences LVCYYTWS (SEQ ID NO:60), FLCTHIIYS (SEQ ID NO:61), IIYSFANIS (SEQ ID NO:62), LKTLLSVGG (SEQ ID NO:63), FIKSVPPFL (SEQ ID NO:64), FDGLDLAWL (SEQ ID NO:65), LYPGRRDKQ (SEQ ID NO:66), YDIAKISQH (SEQ ID NO:67), LDFISIMTY (SEQ ID NO:68), FISIMTYDF (SEQ ID NO:69), FRGQEDASP (SEQ ID NO:70), YAVGYMLRL (SEQ ID NO:71), MLRLGAPAS (SEQ ID NO:72), LAYYEICDF (SEQ ID NO:73), LRGATVHRT (SEQ ID NO:74), YLKDRQLAG (SEQ ID NO:75), LAGAMVWAL (SEQ ID NO:76), VWALDLDDF (SEQ ID NO:77) or LDLDDFQGS (SEQ ID NO:78).

2. Peptide consisting of 16 to 55 amino acid residues, said peptide comprising at least one of the amino acid sequences YKLVCYYTWSQYREG (SEQ ID NO:1), YTSWSQYREGDGSCFP (SEQ ID NO:2), LDRFLCTHIIYSFANI (SEQ ID NO:5), THIIYSFANISNDHID (SEQ ID NO:6), PNLKTLLSVGGWNFGS (SEQ ID NO:12), NTQSRRTFIKSVPPFL (SEQ ID NO:16), TFIKSVPPFLRTHGFD (SEQ ID NO:17), PPFLRTHGFDGLDLAW (SEQ ID NO:18), HGFDGLDLAWLYPGRR (SEQ ID NO:19), DLAWLYPGRRDKQHFT (SEQ ID NO:20), TIDSSYDIAKISQHLD (SEQ ID NO:28), DIAKISQHLD FISIMT (SEQ ID NO:29), QHLD FISIMTYDFHGA (SEQ ID NO:30), SPLFRGQEDASPDRFS (SEQ ID NO:34), DYAVGYMLRLGAPASK (SEQ ID NO:37), MLRLGAPASKLVMGIP (SEQ ID NO:38), PASKLVMGIPTFGRSF (SEQ ID NO:39), GTLAYYEICDFLRGAT (SEQ ID NO:46), EICDFLRGATVHRTL (SEQ ID NO:47), RGATVHRTL GQQVPYA (SEQ ID NO:48), VKSKVQYLKDRQLAGA (SEQ ID NO:53), YLKDRQLAGAMVWALD (SEQ ID NO:54), LAGAMVWALDLDDFQGS (SEQ ID NO:55).

WALDLDDDFQGSFCGQD (SEQ ID NO:56) or DFQGSFCGQDLRFPLT (SEQ ID NO:57).

3. Peptide according to claim 1 or 2, said peptide comprising at least one of the amino acid sequences YKLVCYYTSWSQYREG (SEQ ID NO:1), YTSWSQYREGDGSCFP (SEQ ID NO:2), LDRFLCTHIIYSFANI (SEQ ID NO:5), THIIYSFANISNDHID (SEQ ID NO:6), PNLKTLLSVGGWNFGS (SEQ ID NO:12), QHLDFISIMTYDFHGA (SEQ ID NO:30), SPLFRGQEDASPDRFS (SEQ ID NO:34), DYAVGYMLRLGAPASK (SEQ ID NO:37), MLRLGAPASKLVMGIP (SEQ ID NO:38), YLKDRQLAGAMVWALD (SEQ ID NO:54) or LAGAMVWALDLDDDFQG (SEQ ID NO:55).
4. Peptide according to any of claims 1 to 3, said peptide comprising at least one of the amino acid sequences YTSWSQYREGDGSCFP (SEQ ID NO:2), SPLFRGQEDASPDRFS (SEQ ID NO:34), MLRLGAPASKLVMGIP (SEQ ID NO:38), YLKDRQLAGAMVWALD (SEQ ID NO:54) or LAGAMVWALDLDDDFQG (SEQ ID NO:55).
5. Hexadecapeptide according to claim 1 to 4, said hexadecapeptide consisting of one of the amino acid sequences YKLVCYYTSWSQYREG (SEQ ID NO:1) YTSWSQYREGDGSCFP (SEQ ID NO:2), LDRFLCTHIIYSFANI (SEQ ID NO:5), THIIYSFANISNDHID (SEQ ID NO:6), PNLKTLLSVGGWNFGS (SEQ ID NO:12), QHLDFISIMTYDFHGA (SEQ ID NO:30), SPLFRGQEDASPDRFS (SEQ ID NO:34), DYAVGYMLRLGAPASK (SEQ ID NO:37), MLRLGAPASKLVMGIP (SEQ ID NO:38), YLKDRQLAGAMVWALD (SEQ ID NO:54) or LAGAMVWALDLDDDFQG (SEQ ID NO:55).
6. Peptide according to any of the claims 1 to 5 for use as a medical substance.

7. Pharmaceutical composition comprising one or more peptides according to any of the claims 1 to 5, and a pharmaceutical acceptable carrier.
8. A diagnostic method for the detection of activated autoreactive T cells comprising the following steps: a) isolation of the peripheral blood mononuclear cells (PBMC) from a blood sample of an individual, b) culture of said PBMC under suitable conditions, c) incubation of said PBMC culture in the presence of one or more peptides according to any of the claims 1 to 5, and d) detection of a response of T cells, for example a proliferative response, indicating the presence of activated autoreactive T cells in the individual.
9. Testkit, for the detection of activated autoreactive T cells, said test kit comprising one or more peptides according to any of the claims 1 to 5.

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original first and joint inventor (if plural names are listed below) of the subject matter for which a patent is sought on the invention entitled: *"Novel peptides suitable for use in antigen specific immunosuppressive therapy"*

the specification of which

[CHECK ONE]

☐ is attached hereto

☐ was filed on \_\_\_\_\_ as Application Serial

No. \_\_\_\_\_ and was amended on \_\_\_\_\_

[if applicable]

☒ as filed under the Patent Cooperation Treaty on APRIL-22-1997

Serialno. PCT/EP 97/02051, The United States of America being designated.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined Title 37, Code of Federal Regulations Section 1.56(a)

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign applications(s) for patent or inventor's certificate having a filing date before that of the application(s) on which priority is claimed:

| Prior Foreign Application(s) |                             |                             | Priority claimed |         |
|------------------------------|-----------------------------|-----------------------------|------------------|---------|
| <u>96201106.0</u>            | <u>EP</u>                   | <u>24-04-1996</u>           | <u>V</u> Yes     | ____ No |
| Number                       | Country                     | Day/Month/Year filed        | ____ Yes         | ____ No |
| <u>                    </u>  | <u>                    </u> | <u>                    </u> | ____ Yes         | ____ No |
| <u>                    </u>  | <u>                    </u> | <u>                    </u> | ____ Yes         | ____ No |
| Number                       | Country                     | Day/Month/Year filed        | ____ Yes         | ____ No |

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, Section

Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application.

Pending

(U.S. Serial No.) (Filing date) (Status-patented, pending, abandoned)  
Pending

(U.S. Serial No. (Filing date) (Status-patented, pending, abandoned)

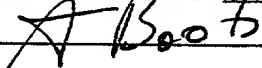
And I hereby appoint as principal attorneys, William M. Blackstone, Registration No. 29,772, Mary E. Gormley, Registration No. 34,409 and Gregory R. Muir, Registration No. 35,293, as patent agent.

Please address all communications to:

William M. Blackstone  
AKZO NOBEL  
1300 Piccard Drive #206  
Rockville, MD 20850-4373

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.


Full name of sole or first inventor Anna Maria Helena Boots

Inventor's signature  18th September  
Date 1998

Citizenship Dutch

Residence and P.O. Address Verlengde Torenstraat 10, 5366 AV Megen, The Netherlands

Full name of second joint inventor Gisbertus Franciscus Maria Verheijden

Inventor's signature  18th September  
Date 1998

Citizenship Dutch

Residence and P.O. Address Heischouw 7, 5345 XT Oss, The Netherlands

Full name of third joint inventor

Inventor's signature \_\_\_\_\_  
Date \_\_\_\_\_

Citizenship \_\_\_\_\_

Residence and P.O. Address \_\_\_\_\_

Full name of fourth joint inventor

Inventor's signature \_\_\_\_\_  
Date \_\_\_\_\_

Citizenship \_\_\_\_\_

Residence and P.O. Address \_\_\_\_\_

# SEQUENCE LISTING

<110> BOOTS, ANNA M.H. .  
VERHEIJDEN, GILBERTUS F.M.

<120> NOVEL PEPTIDES SUITABLE FOR USE IN ANTIGEN SPECIFIC  
IMMUNOSUPPRESSIVE THERAPY

<130> O/96198 US

<140> PCT/EP97/02051

<141> 1997-04-22

<160> 78

<170> PatentIn Ver. 2.0

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SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

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| Tyr | Lys | Leu | Val | Cys | Tyr | Tyr | Thr | Ser | Trp | Ser | Gln | Tyr | Arg | Glu | Gly |
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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Thr | Ser | Trp | Ser | Gln | Tyr | Arg | Glu | Gly | Asp | Gly | Ser | Cys | Phe | Pro |
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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Arg | Glu | Gly | Asp | Gly | Ser | Cys | Phe | Pro | Asp | Ala | Leu | Asp | Arg | Phe |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Cys | Phe | Pro | Asp | Ala | Leu | Asp | Arg | Phe | Leu | Cys | Thr | His | Ile | Ile |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Asp | Arg | Phe | Leu | Cys | Thr | His | Ile | Ile | Tyr | Ser | Phe | Ala | Asn | Ile |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

<210> 6

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 6

Thr His Ile Ile Tyr Ser Phe Ala Asn Ile Ser Asn Asp His Ile Asp  
1 5 10 15

<210> 7

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 7

Phe Ala Asn Ile Ser Asn Asp His Ile Asp Thr Trp Glu Trp Asn Asp  
1 5 10 15

<210> 8

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 8

Asp His Ile Asp Thr Trp Glu Trp Asn Asp Val Thr Leu Tyr Gly Met  
1 5 10 15

<210> 9

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 9

Glu Trp Asn Asp Val Thr Leu Tyr Gly Met Leu Asn Thr Leu Lys Asn  
1 5 10 15

<210> 10

<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 10

Leu Tyr Gly Met Leu Asn Thr Leu Lys Asn Arg Asn Pro Asn Leu Lys  
1 5 10 15

<210> 11

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 11

Thr Leu Lys Asn Arg Asn Pro Asn Leu Lys Thr Leu Leu Ser Val Gly  
1 5 10 15

<210> 12

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 12

Pro Asn Leu Lys Thr Leu Leu Ser Val Gly Gly Trp Asn Phe Gly Ser  
1 5 10 15

<210> 13

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM

# SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 13

Leu Ser Val Gly Gly Trp Asn Phe Gly Ser Gln Arg Phe Ser Lys Ile  
1 5 10 15

<210> 14

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 14

Asn Phe Gly Ser Gln Arg Phe Ser Lys Ile Ala Ser Asn Thr Gln Ser  
1 5 10 15

<210> 15

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 15

Phe Ser Lys Ile Ala Ser Asn Thr Gln Ser Arg Arg Thr Phe Ile Lys  
1 5 10 15

<210> 16

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 16

Asn Thr Gln Ser Arg Arg Thr Phe Ile Lys Ser Val Pro Pro Phe Leu  
1 5 10 15

<210> 17  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 17  
Thr Phe Ile Lys Ser Val Pro Pro Phe Leu Arg Thr His Gly Phe Asp  
1 5 10 15

<210> 18  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 18  
Pro Pro Phe Leu Arg Thr His Gly Phe Asp Gly Leu Asp Leu Ala Trp  
1 5 10 15

<210> 19  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 19  
His Gly Phe Asp Gly Leu Asp Leu Ala Trp Leu Tyr Pro Gly Arg Arg  
1 5 10 15

<210> 20  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 20

Asp Leu Ala Trp Leu Tyr Pro Gly Arg Arg Asp Lys Gln His Phe Thr  
1 5 10 15

<210> 21

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 21

Pro Gly Arg Arg Asp Lys Gln His Phe Thr Thr Leu Ile Lys Glu Met  
1 5 10 15

<210> 22

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 22

Gln His Phe Thr Thr Leu Ile Lys Glu Met Lys Ala Glu Phe Ile Lys  
1 5 10 15

<210> 23

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 23

Ile Lys Glu Met Lys Ala Glu Phe Ile Lys Glu Ala Gln Pro Gly Lys

1 5 10 15

<210> 24  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 24  
Glu Phe Ile Lys Glu Ala Gln Pro Gly Lys Lys Gln Leu Leu Leu Ser  
1 5 10 15

<210> 25  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 25  
Gln Pro Gly Lys Lys Gln Leu Leu Leu Ser Ala Ala Leu Ser Ala Gly  
1 5 10 15

<210> 26  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 26  
Leu Leu Leu Ser Ala Ala Leu Ser Ala Gly Lys Val Thr Ile Asp Ser  
1 5 10 15

<210> 27  
<211> 16  
<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 27

Leu Ser Ala Gly Lys Val Thr Ile Asp Ser Ser Tyr Asp Ile Ala Lys  
1 5 10 15

<210> 28

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 28

Thr Ile Asp Ser Ser Tyr Asp Ile Ala Lys Ile Ser Gln His Leu Asp  
1 5 10 15

<210> 29

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 29

Asp Ile Ala Lys Ile Ser Gln His Leu Asp Phe Ile Ser Ile Met Thr  
1 5 10 15

<210> 30

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 30

Gln His Leu Asp Phe Ile Ser Ile Met Thr Tyr Asp Phe His Gly Ala  
1 5 10 15

<210> 31

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 31

Ser Ile Met Thr Tyr Asp Phe His Gly Ala Gln Arg Gly Thr Thr Gly  
1 5 10 15

<210> 32

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 32

Phe His Gly Ala Trp Arg Gly Thr Thr Gly His His Ser Pro Leu Phe  
1 5 10 15

<210> 33

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 33

Gly Thr Thr Gly His His Ser Pro Leu Phe Arg Gly Gln Glu Asp Ala  
1 5 10 15

<210> 34

<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 34

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Pro | Leu | Phe | Arg | Gly | Gln | Glu | Asp | Ala | Ser | Pro | Asp | Arg | Phe | Ser |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

<210> 35

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 35

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Glu | Asp | Ala | Ser | Pro | Asp | Arg | Phe | Ser | Asn | Thr | Asp | Tyr | Ala | Val |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

<210> 36

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 36

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Arg | Phe | Ser | Asn | Thr | Asp | Tyr | Ala | Val | Gly | Tyr | Met | Leu | Arg | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

<210> 37

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM

# SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 37

Asp Tyr Ala Val Gly Tyr Met Leu Arg Leu Gly Ala Pro Ala Ser Lys  
1 5 10 15

<210> 38

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 38

Met Leu Arg Leu Gly Ala Pro Ala Ser Lys Leu Val Met Gly Ile Pro  
1 5 10 15

<210> 39

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 39

Pro Ala Ser Lys Leu Val Met Gly Ile Pro Thr Phe Gly Arg Ser Phe  
1 5 10 15

<210> 40

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 40

Met Gly Ile Pro Thr Phe Gly Arg Ser Phe Thr Leu Ala Ser Ser Glu  
1 5 10 15

<210> 41  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 41

Gly Arg Ser Phe Thr Leu Ala Ser Ser Glu Thr Gly Val Gly Ala Pro  
1 5 10 15

<210> 42  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 42

Ala Ser Ser Glu Thr Gly Val Gly Ala Pro Ile Ser Gly Pro Gly Ile  
1 5 10 15

<210> 43  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 43

Val Gly Ala Pro Ile Ser Gly Pro Gly Ile Pro Gly Arg Phe Thr Lys  
1 5 10 15

<210> 44  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 44

Gly Pro Gly Ile Pro Gly Arg Phe Thr Lys Glu Ala Gly Thr Leu Ala  
1 5 10 15

<210> 45

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 45

Arg Phe Thr Lys Glu Ala Gly Thr Leu Ala Tyr Tyr Glu Ile Cys Asp  
1 5 10 15

<210> 46

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 46

Gly Thr Leu Ala Tyr Tyr Glu Ile Cys Asp Phe Leu Arg Gly Ala Thr  
1 5 10 15

<210> 47

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 47

Glu Ile Cys Asp Phe Leu Arg Gly Ala Thr Val His Arg Thr Leu Gly

1 5 10 15

<210> 48  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 48

Arg Gly Ala Thr Val His Arg Thr Leu Gly Gln Gln Val Pro Tyr Ala  
1 5 10 15

<210> 49  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 49

Arg Thr Leu Gly Gln Gln Val Pro Tyr Ala Thr Lys Gly Asn Gln Trp  
1 5 10 15

<210> 50  
<211> 16  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 50

Val Pro Tyr Ala Thr Lys Gly Asn Gln Trp Val Gly Tyr Asp Asp Gln  
1 5 10 15

<210> 51  
<211> 16  
<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 51

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Asn | Gln | Trp | Val | Gly | Tyr | Asp | Asp | Gln | Glu | Ser | Val | Lys | Ser | Lys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

<210> 52

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 52

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Asp | Asp | Gln | Glu | Ser | Val | Lys | Ser | Lys | Val | Gln | Tyr | Leu | Lys | Asp |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

<210> 53

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 53

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Lys | Ser | Lys | Val | Gln | Tyr | Leu | Lys | Asp | Arg | Gln | Leu | Ala | Gly | Ala |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

<210> 54

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 54

Tyr Leu Lys Asp Arg Gln Leu Ala Gly Ala Met Val Trp Ala Leu Asp  
1 5 10 15

<210> 55

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 55

Leu Ala Gly Ala Met Val Trp Ala Leu Asp Leu Asp Asp Phe Gln Gly  
1 5 10 15

<210> 56

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 56

Trp Ala Leu Asp Leu Asp Asp Phe Gln Gly Ser Phe Cys Gly Gln Asp  
1 5 10 15

<210> 57

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 57

Asp Phe Gln Gly Ser Phe Cys Gly Gln Asp Leu Arg Phe Pro Leu Thr  
1 5 10 15

<210> 58

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 58

Cys Gly Gln Asp Leu Arg Phe Pro Leu Thr Asn Ala Ile Lys Asp Ala  
1 5 10 15

<210> 59

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 59

Leu Arg Phe Pro Leu Thr Asn Ala Ile Lys Asp Ala Leu Ala Ala Thr  
1 5 10 15

<210> 60

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 60

Leu Val Cys Tyr Tyr Thr Ser Trp Ser  
1 5

<210> 61

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM

SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 61

Phe Leu Cys Thr His Ile Ile Tyr Ser

1

5

<210> 62

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 62

Ile Ile Tyr Ser Phe Ala Asn Ile Ser

1

5

<210> 63

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 63

Leu Lys Thr Leu Leu Ser Val Gly Gly

1

5

<210> 64

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 64

Phe Ile Lys Ser Val Pro Pro Phe Leu

1

5

<210> 65

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 65

Phe Asp Gly Leu Asp Leu Ala Trp Leu  
1 5

<210> 66

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 66

Leu Tyr Pro Gly Arg Arg Asp Lys Gln  
1 5

<210> 67

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 67

Tyr Asp Ile Ala Lys Ile Ser Gln His  
1 5

<210> 68

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 68

Leu Asp Phe Ile Ser Ile Met Thr Tyr

1

5

<210> 69

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 69

Phe Ile Ser Ile Met Thr Tyr Asp Phe

1

5

<210> 70

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 70

Phe Arg Gly Gln Glu Asp Ala Ser Pro

1

5

<210> 71

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 71

Tyr Ala Val Gly Tyr Met Leu Arg Leu

1

5

<210> 72

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 72

Met Leu Arg Leu Gly Ala Pro Ala Ser

1

5

<210> 73

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 73

Leu Ala Tyr Tyr Glu Ile Cys Asp Phe

1

5

<210> 74

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 74

Leu Arg Gly Ala Thr Val His Arg Thr

1

5

<210> 75

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 75

Tyr Leu Lys Asp Arg Gln Leu Ala Gly  
1 5

<210> 76

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 76

Leu Ala Gly Ala Met Val Trp Ala Leu  
1 5

<210> 77

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 77

Val Trp Ala Leu Asp Leu Asp Asp Phe  
1 5

<210> 78

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DERIVED FROM  
SEQUENCE OF HUMAN CARTILAGE (HC) -39 PROTEIN

<400> 78

Leu Asp Leu Asp Asp Phe Gln Gly Ser

1

5